REMARKS

Claims 1-38 were previously pending in this application. Claims 4-38 have been withdrawn from consideration as being drawn to non-elected subject matter. By this amendment, Claims 4-38 have been cancelled without prejudice to the filing of any appropriate divisional/continuation application as being directed to non-elected subject matter. New claims 39-56 also have been added to claim additional embodiments of the invention. Support for these claims is found *inter alia* on page 9, lines 22-28, page 20, line 23 to page 21, line 2 and page 21, line 29 to page 22, line 5. No new matter has been added.

Claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-3 stand rejected under 35 U.S.C. § 102(b), as being anticipated by Kallioniemi et al. (1994) *Proc. Natl. Acad. Sci. U.S.A.* 91:2156. Claims 1-3 stand rejected under 35 U.S.C. § 102(b), as being anticipated by Lavi, WO 97/10796.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Specifically, claim 1 was amended to recite a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3. Support for this amendment can be found in the published specification at least at paragraph [0082] where Applicants teach a polynucleotide that has a sequence identity of at least 70% compared to a reference sequence, at page 27, where Applicants teach the human WIP1 open reading frame sequence set forth as SEQ ID NO:1, and at page 14, where Applicants teach the human WIP1 gene sequence set forth as SEQ ID NO:3. Claim 1 was further amended to replace "biological subject" with "biological sample" for clarity.

Applicants also have presented new claims 39-56 for consideration. Claims 39-41 are dependent claims which increase the level of sequence identity to 90%. Claims 42-44 are dependent claims which increase the level of sequence identity to 95%. Claims 45-47 are dependent claims which specify the actual sequence of SEQ IDs 1 and 3. Claims 48-56 are parallel dependent claims that direct the claims to SEQ ID No. 1 only.

The amendments presented herein add no new matter and do not raise new issues requiring further search. Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place this case in condition for allowance.

Claims 1-3 Are Enabled

At page 4, section 6 of the instant Office Action, claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for diagnosing breast cancer in a human, comprising detecting and measuring the human WIP1 gene, SEQ ID NO:1, copy number in human breast tissue that is suspected to be cancerous, thereby generating data for a test gene copy number, and comparing the test gene copy number to data for a control gene copy number, wherein about a 2.5 fold or greater amplification of the gene in the human breast tissue relative to the control indicates the presence of breast cancer in the human, does not reasonably provide enablement for diagnosing *any* cancer in *any* mammal by measuring and detecting *any* amplification in the gene copy number of *any* "WIP1" gene in *any* biological subject that is suspected to be cancerous. The Office Action states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection based on the amended claims now presented.

35 U.S.C. § 112, first paragraph requires that the specification must enable a person skilled in the art to make and use the claimed invention. However, a specification need not, and should not, disclose what is well known in the art. The invention that one skilled in the art must be enabled to make and use is that defined by the claims of the particular application. The issue of adequate enablement depends on whether one skilled in the art could practice the claimed invention without undue experimentation. Enablement is not precluded by the necessity of some experimentation such as routine screening, even if it is extensive routine screening. Also, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01) if the level of skill in the art is high or if all of the methods needed to practice the claimed invention are well known. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1406 (Fed. Cir. 1988).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. (Citations omitted). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 U.S.P.Q. 2d at 1404.

The instant Office Action admits that the level of skill in the art is deemed to be high (page 9). The Office Action states that given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the limited amount of working examples and the negative teachings of the prior art balanced only against the high skill level in the art, it would require undue experimentation for one skilled in the art to perform the methods of the instant claims as written. Without acquiescing to the rejection, Applicants respectfully submit that claim 1 has been amended to recite a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3 (and in the new dependent claims to 90%, 95% and the actual sequence).

Applicants respectfully submit that the instant specification teaches the open reading frame of the human WIP1 gene (SEQ ID NO:1) as well as the sequence of the WIP1 gene (SEQ ID NO:3) (pages 27 and 14 of the published application, respectively). The specification teaches that sequence identity may be determined using standard parameters, and teaches that a percentage of sequence identity may be determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions, substitutions or deletions for optimal alignment of the two sequences (paragraphs [0081] and [0082] of the published application). The percentage is then calculated by determining the number of positions at which the identical nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity (paragraph [0082] of the published application).

Applicants teach that a variety of routine techniques, such as hybridization-based and

amplification-based methods, may be used to measure and evaluate DNA copy numbers (paragraph [0168] of the published application). Examples of suitable hybridization-based assays include Southern blots, fluorescence *in situ* hybridization and comparative genomic hybridization (paragraphs [0154] – [0156] of the published application). Examples of suitable amplification-based assays include quantitative amplification such as real-time quantitative PCR, ligase chain reaction, transcription amplification, self-sustained sequence replication, dot PCR, linker adapter PCR, and microarray-based platforms (paragraphs [0158] – [0160] of the published application). Applicants also provide a working example using DNA microarrays (e.g., using TaqMan probes) to identify WIP1 gene amplification in tissues and cells (paragraphs [0229] - [0232] of the published application).

The Office Action states that the teachings of the specification do not address an association of the amplification of the WIP1 gene with *any* type of cancer and the teachings with regard to the amplification of the WIP1 gene in colon, prostate, lung and ovarian tumors indicate, in fact, that there is not an association of the amplification of the WIP1 gene with *any* type of cancer (page 7). Applicants have demonstrated WIP1 gene amplification in breast and lung primary tumor samples (Table 2). The results in Table 2 do not necessarily mean that the WIP1 gene is not amplified in colon, metastatic prostate or ovary tumor samples, only that an amplification was not detected in this data set. The cutoff for amplification in Table 2 is 2.5X. Accordingly, an amplification of 2.4X, for example, would not be recorded as amplified when, in fact it was. In this regard, it is important to note that WIP1 overexpression *was* detected in colon, metastatic prostate and ovary tumor samples. In addition, Applicants have demonstrated the involvement of the WIP1 gene in fibroblast transformation and release from cell death. Applicants have shown that the WIP1 gene, coexpressed with RAS, can transform primary mouse embryo fibroblasts and can suppress UV-induced apoptosis (paragraphs [0236] and [0237] of the published application).

Based on Applicants' teachings described above, one of skill in the art would readily be able to ascertain whether a WIP1 gene copy having the claimed sequence identity is increased in a variety of cancers using only routine methods. Nothing more should be necessary to enable the claimed methods. For at least these reasons, Applicants' specification, coupled with the level of

skill in the art, enables a person of skill in the art to make and/or use the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

The Specification Provides Adequate Written Description for Claims 1-3

At page 10, section 7 of the instant Office Action, claims 1-3 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that the claims are drawn to method of diagnosing a cancer in a mammal comprising detecting and measuring the WIP1 gene copy number in a biological subject suspected to be precancerous or cancerous. The Office Action states that, while the specification has taught methods of diagnosing a cancer in a human comprising detecting and measuring the human WIP1 (SEQ ID NO:1) gene copy number in a biological subject, the claims encompass methods of diagnosing a cancer in a mammal comprising detecting and measuring the gene copy number of a large genus of variant and homolog genes with homology to WIP1 in a biological subject which have not been taught or described in the specification. Applicants respectfully traverse this rejection based on the amended claims now presented.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). With respect to polypeptides, the U.S. Patent and Trademark Office's Written Description Guidelines state:

> The written description requirement for a claimed genus may be

> satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . .

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal reference omitted, approved in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d (BNA) 1609, 1613 (Fed. Cir. 2002) (emphasis added).

Applicants respectfully submit that the specification more than adequately describes the claimed methods with reasonable clarity to one of skill in the art. As described above, Applicants teach the identity of a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3 (as well as 90%, 95% and the actual sequence), and describe a variety of methods in which a gene copy number may be detected and measured. Thus, one of skill in the art would recognize that the specification adequately describes the claimed method.

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). The knowledge of one skilled in the art also must be considered, because the specification must "indicate[s] to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q.2d (BNA) 1945, 1948 (Fed. Cir. 2002). The Office Action admits, at page 9, that the level of skill in the art is deemed to be high. When read as a whole, taking into account the knowledge of persons skilled in the art at the filing date of the application, this specification indicates to those skilled in the art that Applicants had possession of the claimed subject matter at the time of filing. Accordingly, Applicants request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement be reconsidered and withdrawn.

Claims 1-3 Are Definite

At page 13, section 8 of the instant Office Action, claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action states that the preamble of instant claim 1 recites "a method for diagnosing cancer," while the claim finally recites "wherein an amplification of the gene in the biological sample indicates the presence of a ***precancerous lesion or a cancer*** in the mammal." The Office Action concludes that the intent of instant claim 1 is not clear because it is not clear whether the intent is to diagnose a cancer only or to diagnose a precancerous lesion as well. The Office Action requires clarification. Applicants respectfully traverse this rejection based on the amended claims now presented.

Without acquiescing to the rejection, Applicants respectfully submit that claim 1 has been amended to recite a method for diagnosing a ***precancerous lesion or*** a cancer in a mammal to clarify that the claim is directed to a method for diagnosing either a cancer or a precancerous lesion. Accordingly, Applicants respectfully request that this rejection of claims 1-3 under 35 U.S.C. § 112, second paragraph, as being indefinite be reconsidered and withdrawn.

Claims 1-3 Are Novel Over Kallioniemi et al.

At page 14, section 10 of the instant Office Action, claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kallioniemi et al. (1994) *Proc. Natl. Acad. Sci. U.S.A.* 91:2156, as defined by Wu et al. (2001) 61:4951. The Office Action states that Kallioniemi et al. teaches a method of detecting and measuring DNA sequence copy number increases for the 17q22-23 region in several human primary breast tumors and breast cancer cell lines. The Office Action also states that Kallioniemi et al. teaches that copy number increases of the 17q22-24 region were found in 18% of primary breast tumors and 67% of breast cancer cell lines examined. The Office Action further states that this method taught by Kallioniemi et al. involves comparative genomic hybridization in which the relative intensity of a fluorescent signal from a test chromosome (from tumor cells for example) hybridized with a labeled probe is compared to the intensity of a fluorescent signal from a control chromosome hybridized with the same probe

that emits a different fluorescent color. Applicants respectfully traverse this rejection.

Claims 1 and claims depending therefrom are directed in part to a method for diagnosing a precancerous lesion or a cancer comprising detecting and measuring gene copy number of a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3. The pending claims are based on Applicants' novel discovery that WIP1 is overexpressed in a variety of cancers including breast cancer, lung cancer, prostate cancer, ovarian cancer and colon cancer (published application, paragraph [0018]).

Kallioniemi et al. fails to teach or suggest the claimed invention. Kallioniemi et al. is directed to the identification and mapping of ***chromosomal regions*** having an increased DNA sequence copy number (abstract). Kallioniemi et al. does not identify any individual genes or investigate specific genes, and instead is interested in providing an "***overview*** of copy-number changes occurring in solid tumors" and identifies ***chromosomal subregions*** that may be associated with breast cancer (page 2159, left column, first paragraph of discussion, emphasis added). Kallioniemi et al. provides no specific teaching that a WIP1 gene or a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3 has any association with breast cancer. Kallioniemi et al. merely teaches that chromosomal regions including 17q22-q24 are amplified in certain breast cancer cell lines and primary tumors (abstract).

The Office Action uses Wu et al. to define Kallioniemi et al., and states that Wu teaches that the human WIP1 gene is located in the 17q22-24 region of chromosome 17 (page 14, section 10). Wu et al. is directed to the identification of targets of amplification in breast cancer cell lines and tumors on chromosome 17q22-23 (abstract). Applicants respectfully point out that Wu et al. is dated **July 1, 2001**, and that the subject matter of the claimed invention claims priority to provisional application number 60/268,362, filed **February 14, 2001**. In the provisional application, Applicants teach that WIP1 DNA is frequently amplified in ***cancer cells***, and that the WIP1 gene can be used to ***diagnose tumors and cancers*** including ***breast cancer*** (page 3, line 29 to page 4, line 4). Accordingly, Wu et al. is not proper prior art and should not be used to supplement the teachings of Kallioniemi et al.

For at least these reasons, Applicants respectfully request that the rejection of claims 1-3

under 35 U.S.C. § 102(b) as being anticipated by Kallioniemi et al. be reconsidered and withdrawn.

Claims 1-3 Are Novel Over Lavi

At page 15, section 11 of the instant Office Action, claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lavi, WO 97/10796. The Office Action states that, regarding instant claim 1, "gene copy number" has been given the broad interpretation of the relative number of copies of the DNA sequence that encodes the products of the gene or any RNA expression products encoded by the gene. The Office Action states that Lavi teaches a method of detecting cancer in a patient by detecting alterations in gene activity of the protein phosphatase 2Calpha gene, a member of the same family of phosphatases as WIP1 (broadly interpreted as a WIP1 homolog as broadly defined by the specification on pages 21 and 22), and genetic polymorphisms thereof in a specimen isolated from the patient wherein the gene activity of the patient is compared to normal controls. The Office Action also states that Lavi teaches that samples used with the above method can be biopsied material from suspected precancerous lesions of any tissue or bodily fluid which can be assayed for PP2Calpha activity or gene product. Applicants respectfully traverse this rejection.

The Lavi reference fails to teach or suggest the claimed invention. The Lavi reference is directed to methods of detecting cancer in a patient by detecting alterations of the activity of the gene (PP2Cα or PP2Cβ) coding for human type protein phosphatase 2C (page 5, line 33 to page 6, line 2). WIP1 cDNA shows limited similarity to other PP2C phosphatases except in three conserved regions, which have ***50-77% sequence identity only within the conserved region*** (Fiscella et al. (1997 *Proc. Natl. Acad. Sci. USA* 94:6048, page 6050, first partial paragraph and Figure 1). The Lavi reference neither teaches nor suggests a method of diagnosing a precancerous lesion or a cancer by detecting and measuring gene copy number of a WIP1 gene or a method of diagnosing a precancerous lesion or a cancer by detecting and measuring gene copy number of a WIP1 gene having a nucleotide sequence homology of at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:3. Accordingly, Applicants respectfully request that the

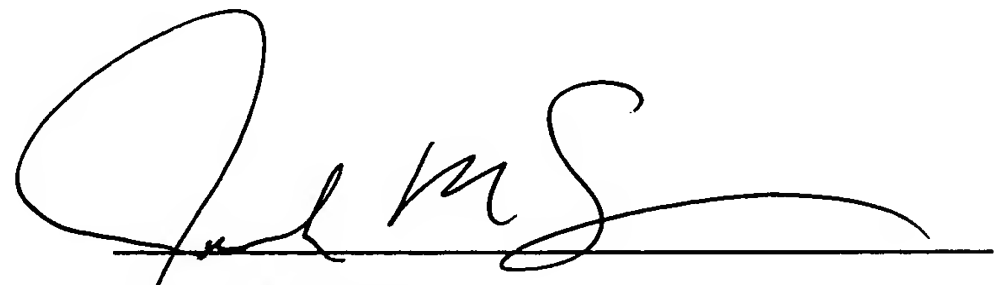
rejection of claims 1-3 under 35 U.S.C. § 102(b) as being anticipated by Lavi be reconsidered and withdrawn.

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

Date: November 18, 2005



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